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Investigating the association between medication adherence and health-related quality of life in COPD: Methodological challenges when using a proxy measure of adherence

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ABSTRACT

Background: The association between non-adherence to medication and health-related quality-of-life (HRQoL) in Chronic Obstructive Pulmonary Disease (COPD) remains poorly understood. Different ways to deal with methodological challenges to estimate this association have probably contributed to conflicting results.

Aim: To investigate the association between medication adherence and HRQoL, thereby illustrating methodological challenges that need to be addressed.

Methods: We used longitudinal patient-level data from a cluster-randomized controlled trial (i.e. RECODE) including three-year data on type and dose of COPD maintenance medication prescribed and HRQoL (Clinical COPD Questionnaire [CCQ], st. George Respiratory Questionnaire [SGRQ], EuroQol 5-dimensions [EQ-5D]) of 511 patients. A linear mixed model was used to assess the association between adherence and HRQoL using a fixed cut-off of 80% of the proportion of days covered (PDC) to define adherence. Subsequently, we investigated the impact of differences in disease severity; lifestyle; and reversed causality, representing the methodological challenges. Additionally, we investigated the impact of changing the definition of adherence.

Results: In unadjusted analyses, and analyses adjusting for demographic characteristics only, SGRQ score was worse in the adherent compared to the non-adherent group. This association disappeared when correcting for disease severity and/or lifestyle. A better SGRQ score was predictive of decreased adherence in the following year. However, accounting for the previous HRQoL did not result in positive associations between adherence and HRQoL. When defining four categories of adherence, patients with a PDC between 80 and 99% had a significantly worse SGRQ score compared to patients with a PDC <60%, even after correction for lifestyle. There was no significant association between adherence and CCQ or EQ-5D.

Conclusion: This study showed persistent methodological challenges in the investigation of the effect of medication adherence on HRQoL in COPD. A positive association of adherence and HRQoL was not found, even after adjusting for lifestyle, disease severity, and previous HRQoL.

1. Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, the two major goals in the treatment of Chronic Obstructive Pulmonary Disease (COPD) are the prevention

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of exacerbations and the optimization of health-related quality of life (HRQoL) [1]. Besides smoking cessation and other non-pharmacologic treatment, medication plays an important role in the current treatment of COPD. The efficacy of currently available maintenance medication for COPD has been shown in numerous studies, mainly performed in well-controlled settings with highly motivated patients and who demonstrate good medication adherence [2,3]. However, medication adherence is considerable lower in daily practice [4–6]. Hence, the positive results found in randomized controlled clinical trials may be less in real-life [4–6]. Two recent reviews evaluated the consequences of non-adherence for HRQoL in patients with COPD [7,8]. They found that at least 50% of the studies reported no or negative associations between medication adherence and HRQoL and they concluded that the association between non-adherence and HRQoL remains poorly understood. Researchers are facing several methodological challenges such as the possibility of confounding by disease severity, healthy lifestyle, and reversed causality. Different ways to overcome these challenges have probably contributed to the conflicting results that were reported with respect to the direction of the association (positive or negative) [7,8]. A more systematic comparison of different methods to deal with these challenges might contribute to a better understanding of the causal pathway of the association between adherence and HRQoL and would allow tailored interventions to optimize COPD treatment.

We used longitudinal patient-level data from the RECODE study, the largest 2-year cluster randomized trial in 40 primary care groups (N = 1086) comparing a COPD disease management program with usual care, to investigate the association between medication adherence and HRQoL [9,10]. As part of this trial, data on medication prescribed during the 2-year trial period as well as the year prior to the trial were extracted from the general practitioners' (GP) electronic medical records (EMR). During the same 2-year period, patients' HRQoL was periodically assessed as part of the trial. Hence, the RECODE-dataset provides a unique opportunity to investigate the association between medication adherence and HRQoL, while systematically investigating the role of disease severity and healthy lifestyle in this association. The dataset also allowed us to study reversed causality, i.e. whether adherence in a particular year was influenced by HRQoL in the year before.

2. Methods

2.1. Study population

RECODE was a two-year cluster randomized trial including 20 primary care teams who were randomized to the intervention group that implemented an integrated care program and 20 teams who were randomized to the usual care group. From these 40 teams we recruited 1086 patients with physician-diagnosed COPD according to the GOLD guidelines [1] between 2010 and 2011. Exclusion criteria were terminal illnesses, dementia, cognitive impairment, inability to complete questionnaires in Dutch, and hard drug or alcohol abuse. Other co-morbidity was not an exclusion criterion. The COPD patients in the RECODE trial were found to be representative of the COPD population treated in primary care in the Netherlands, i.e. the enrolled patients were mainly elderly, (ex) smokers, had moderate COPD which was reflected by a mean post-bronchodilator Forced expiratory volume in 1 (FEV1) of 68% predicted, and substantial co-morbidities [9]. All participants provided written informed consent before participation and the RECODE study was approved by the medical ethics committee of the Leiden University Medical Centre (Netherlands Trial Register [NTR] NTR2268).

For the current study, we included all RECODE patients from 23 of the 40 RECODE primary care groups with at least two prescriptions for COPD maintenance medication in one year and complete HRQoL records in that same year. Patients from the intervention group as well as the control group were included. The remaining practices and patients were excluded because data on type of medication and dosage prescribed could not be extracted from the EMRs.

2.2. Drug adherence

The COPD maintenance medication included long-acting β2-agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), or fixed-dose LABA/ICS combinations. Medication prescriptions and prescribed daily doses were extracted from the EMR of the GPs. For each year, adherence was calculated as the proportion of days covered (PDC), defined as the proportion of days in a year that a patient had COPD medication available. This is calculated by the sum of all drug doses supplied divided by the daily dosing regimen, divided by 365 days. This method is used in various previous adherence studies in COPD [11–13]. For prescriptions extending beyond the end of the analysis period, the days covered were truncated at the end of the period. The average PDC was used if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations). Patients were classified as adherent if their (average) PDC equalled or exceeded 80%. This threshold is frequently used in adherence studies, also in COPD [12,14–17]. In sensitivity analyses, we investigate the impact of changing the definition of adherence by using (i) a categorical variable with four categories of PDC, i. e <60%, 60–79%, 80–99%, >99%, (ii) PDC as a continuous variable, and (iii) the minimum (or maximum) PDC if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations).

2.3. Data collection

We used the following variables in our analysis:

- HRQoL, which was measured using the Clinical COPD Questionnaire (CCQ) [18,19], the Saint George's Respiratory Questionnaire (SGRQ) [20,21] and the 3-level EuroQoL-5Dimensions (EQ-5D) [22] at baseline, after 1 year and after 2 years. The first two questionnaires (CCQ and SGRQ) are COPD-specific instruments and the EQ-5D is a generic HRQoL instrument used to calculate utilities. Note that a higher score on SGRQ and CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL. These questionnaires were measured at baseline, 12 and 24 months.
- Socio-demographic factors (age, gender, level of education), which were assessed at baseline.
- Forced expiratory volume in 1 s as percentage of the predicted value (FEV1%pred), which was measured at baseline.
- History of exacerbations (moderate and severe). A moderate exacerbation was defined as a worsening of COPD symptoms that led a patient's clinician to prescribe systemic corticosteroids and/or antibiotics, but did not require hospitalization. This information was extracted from the EMR. A severe exacerbation was defined as a worsening of COPD symptoms that required a hospital admission. Hospital admissions were obtained from the resource use questionnaires completed by the patients and confirmed by the EMR. The resource use questionnaire was measured at baseline, 6, 9, 12, 18 and 24 months.
- The Medical Research Council (MRC) dyspnoea scale [23]. This was measured at baseline, 12 and 24 months.

- Charlson Comorbidity Index, which was measured at baseline [24].
- Level of physical activity, which was calculated from the International Physical Activity Questionnaire (IPAQ) by multiplying the frequency (in days) and duration (in minutes) of walking, moderate–intensity activities, and vigorous–intensity activities in terms of the energy requirements, to yield a score in metabolic equivalent time (MET) minutes [25]. This was measured at baseline, 12 and 24 months.
- Self-efficacy from the Self-Management Ability Scale-30 (SMAS-30) [26]. This was measured at baseline, 12 and 24 months
- Smoking status (smoker or no smoker), which was measured at baseline, 12 and 24 months.

2.4. Statistical analysis

We investigated the association between adherence during one year with HRQoL at the end of this year, i.e. the association between adherence during the first trial-year and HRQoL at 12 months, and adherence over the second trial-year and HRQoL at 24 months. We used linear mixed models to assess this association using a fixed cut-off of 80% to define adherent (≥80%) and non-adherent patients (<80%). We investigated the interaction between trial-arm and medication adherence to see if both groups in the trial could be combined, i.e. if the impact of adherence to COPD medication on HRQoL was different between the intervention group and the usual care group. Because there was no significant interaction, the data of the two groups were combined. There was no interaction because the RECODE intervention did not specifically target adherence and adherence to COPD medication and (change in) HRQoL in these two groups were comparable (data not shown). The analyses were performed using STATA (version 13) and statistical significance of results were considered at 5% level.

2.5. Base-case analyses

We started with a linear mixed model with a random intercept and no confounders, thereafter, we included age, gender and level of education (0 high education; 1 low education [defined as no or only primary education]), but no other confounders. Subsequently, this simple, though often used analysis, was expanded. First, by controlling for disease severity, second, by controlling for healthy lifestyle and third, by investigating potential reversed causality. These three analyses represent the challenges that researchers are facing when adequately assessing the association between medication adherence and HRQoL [8]. A more detailed description of these challenges is given below.

2.5.1. Challenge 1: adequately correcting for disease severity

It is likely that more severely ill patients have a higher need for medication and as a result they may be more adherent [27,28]. Hence, a correction for differences in disease severity between adherent and non-adherent patients is necessary. Therefore, we estimated a linear mixed model with a random intercept and correction for four indicators of disease severity, i.e. the FEV_1%pred at baseline, the total exacerbation rate (moderate or severe) in the 12 months prior to the adherence measurement, the MRC dyspnoea scale [23] at the start of the adherence measurement and the Charlson comorbidity index at baseline [24].

2.5.2. Challenge 2: addressing a potential healthy-adherer effect

Some studies suggested that therapy adherence is an indicator of overall healthy lifestyle. It is argued that those who take good care of their health in general, by adopting a healthy lifestyle, are more likely to be adherent to medication. Hence, a positive association between adherence and HRQoL could be caused by a healthy lifestyle in general. This is referred to as the "healthy-adherer effect" [12,29]. Therefore, we estimated a linear mixed model with a random intercept and including three variables that are indicators of a healthy lifestyle in general measured at the same time as the HRQoL. These variables were smoking status (smoker or no smoker), level of physical activity and self-efficacy. We hypothesized that a higher score on IPAQ or self-efficacy and non-smoking status would indicate a healthier lifestyle. In this way, we aimed to 'correct' for a possible healthy-adherer effect.

2.5.3. Challenge 3: investigating potential reversed causality

In the previous analyses, we assessed the effect of adherence during a particular year on HRQoL at the end of that same year. However, reversed causality may be present, meaning that HRQoL measured at the beginning of a year may influence adherence to medication during that year. A better HRQoL may improve adherence ("I am feeling good so I need to keep taking my medication"), but it may also lead to a reduction in adherence ("because I am feeling good I need less medication") [30]. To unravel this association, we studied whether an improvement greater than or equal to the minimal clinically important difference (MCID) in HRQoL (≥4 points on the SGRQ [21]; ≥.4 points on the CCQ [19]) during the first trial-year changed the PDC in the second trial-year using a t-test. In addition, we account for the previous HRQoL in a linear model with an unstructured covariance matrix for repeated measures.

3. Results

3.1. Dataset characteristics

The 23 primary care groups that had complete EMR regarding type and dosage of medication prescribed, enrolled 658 patients into the RECODE trial (61% of all patients in the trial). From these 658 patients, we excluded 147 patients (22%) because they did not have at least two prescriptions for COPD maintenance medication in one year and complete HRQoL records in that same year. In total, 511 COPD patients have been included in this study. The patient characteristics were very similar to those in the total RECODE study population (Appendix 1). For each year, we calculated the PDC for the 511 participants. The majority of the COPD patients (>74%) are using LABA/ICS combinations and the average PDC of COPD maintenance medication is 81%, 76%, 78% in respectively year 0, year 1 and year 2 (Appendix 2).

Table 1 presents the patient characteristics of the dataset split into adherent and non-adherent patients. The proportions of patients who were adherent were 63%, 57% and 58% in year 0, 1 and 2, respectively. The proportion of low educated patients was significantly higher in the non-adherent group (49%) compared to the adherent group (38%) in year 0. Furthermore, the adherent group had worse average MRC and SGRQ scores compared to the non-adherent group in year two.

3.2. Base-case analyses

The results of the base-case analyses are shown in Table 2. In the unadjusted analyses the adherent group had worse quality of life than the non-adherent group. In the case of the SGRQ, this difference was statistically significant ($P = 0.034$) and close to clinical-relevance threshold of 4 [21]. This difference diminished after adjusting for the sociodemographic variables age, sex, and education ($P = 0.098$).

Table 1
Patients' characteristics of adherent and non-adherent COPD patients.

Characteristic	Year 0		Year 1		Year 2	
	Non-adherent (PDC<80%) N = 171	Adherent (≥80%) N = 294	Non-adherent (PDC<80%) N = 213	Adherent (≥80%) N = 278	Non-adherent (PDC<80%) N = 197	Adherent (≥80%) N = 272
Age (years) (SD)	67 (11)	68 (11)	68 (11)	68 (10)	67 (11)	68 (10)
Male (%)	45.0	45.9	50.2	50.4	54.8	49.6
Low education (%)	**48.7**	**37.5**[a]	39.0	42.7	39.8	42.7
FEV_1%pred (SD)	67.8 (20.0)	65.1 (20.1)	67.0 (18.1)	65.2 (21.0)	67.7 (17.8)	64.4 (20.3)
Exacerbations (SD)	.42 (.87)	.50 (.99)	.50 (1.04)	.68 (1.19)	1.04 (1.95)	1.42 (2.18)
MRC dyspnoea (SD)	2.1 (1.3)	2.0 (1.3)	2.1 (1.3)	2.3 (1.3)	**2.2 (1.3)**	**2.5 (1.4)**[a]
Charlson comorbidity index (SD)	2.4 (1.2)	2.3 (1.2)	2.3 (1.3)	2.3 (1.1)	2.3 (1.3)	2.3 (1.2)
Total MET minutes (SD)	3114 (4940)	2539 (4921)	3168 (4807)	2716 (4471)	3325 (4462)	2682 (4253)
Self-efficacy (SD)	64.8 (17.7)	65.5 (17.2)	64.2 (16.9)	62.9 (16.8)	66.0 (18.5)	64.2 (16.3)
Smoker (%)	39.6	33.4	30.9	30.2	49.0	43.8
CCQ (SD)	1.54(1.03)	1.41 (.89)	1.49 (.96)	1.53 (.96)	1.72 (.95)	1.88 (1.02)
SGRQ (SD)	35.7 (21.0)	34.6 (19.9)	34.5 (20.9)	35.6 (20.2)	**33.7 (21.5)**	**39.7 (23.5)**[a]
EQ-5D utility (SD)	.74 (.26)	.74 (.27)	.72 (.26)	.72 (.27)	.78 (.25)	.80 (.21)

Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.
[a] Significant (P < 0.05); SD = Standard Deviation; PDC = Proportion of Days Covered; FEV_1%pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; MET = Metabolic Equivalent Time; CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions.

Table 2
Linear mixed models with and without correcting for demographics, disease severity and healthy-lifestyle variables.

		β	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
Dependent variable CCQ											
	Intercept	1.46	<.01	1.30	<.01	1.18	<.01	2.72	<.01	1.88	<.01
	Adherent (PDC ≥ 80%)	**.09**	**.17**	**.07**	**.31**	**.01**	**.84**	**.12**	**.14**	**.07**	**.28**
Demographics	Year 2	.30	<.01	.30	<.01	.21	<.01	.32	<.01	.21	<.01
	Age			.0001	.97	−.01	.02	−.005	.26	−.01	.06
	Men			−.03	.72	.08	.15	−.04	.61	.08	.24
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV_1% pred					−.005	<.01			−.005	.01
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.69
Healthy lifestyle	Physical activity (MET minutes)							−2.1e-5	.04	7.5e-6	.38
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.14	.096	.14	.06
	Observations used in the analysis (N)	825		754		726		542		524	
Dependent variable SGRQ											
	Intercept	33.3	<.01	24.6	<.01	21.9	<.01	58.9	<.01	40.4	<.01
	Adherent (PDC ≥ 80%)	**3.27**	**.03**	**2.58**	**.098**	**.51**	**.67**	**2.29**	**.18**	**1.01**	**.44**
Demographics	Year 2	2.02	.19	2.35	.13	.55	.64	2.94	.11	.36	.80
	Age			.09	.25	−.08	.21	−.03	.73	−.06	.38
	Men			−1.90	.23	1.00	.41	−3.39	.05	−.32	.82
	Low education			10.1	<.01	4.62	<.01	9.28	<.01	4.47	<.01
Disease severity	FEV_1% pred					−.11	<.01			−.15	<.01
	Exacerbations					3.47	<.01			3.71	<.01
	MRC dyspnoea					9.14	<.01			8.36	<.01
	Charlson comorbidity index					1.37	<.01			.77	.18
Healthy lifestyle	Physical activity (MET minutes)							−.001	.02	1.9e-4	.25
	Self-efficacy							−.37	<.01	−.22	<.01
	Smoker							−.52	.78	−.52	.72
	Observations used in the analysis (N)	794		729		704		542		523	
Dependent variable EQ-5D											
	Intercept	.72	<.01	.65	<.01	.80	<.01	.35	<.01	.63	<.01
	Adherent (PDC ≥ 80%)	**.01**	**.77**	**.01**	**.62**	**.02**	**.27**	**.004**	**.85**	**.01**	**.63**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
	Age			.001	.22	.002	.01	.001	.29	.001	.18
	Men			.06	<.01	.04	.03	.07	<.01	−.04	.02
	Low education			−.09	<.01	−.05	<.01	−.08	<.01	−.05	.02
Disease severity	FEV_1% pred					−.0002	.62			−.001	.32
	Exacerbations					−.02	<.01			−.02	.02
	MRC dyspnoea					−.05	<.01			−.04	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							−7.0e-7	.77	−4.6e-6	.05
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.02	.37	−.03	.17
	Observations used in the analysis (N)	827		760		733		555		535	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time, PDC = Proportion of Days Covered.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Table 3
Clinically important difference in HRQoL in the first trial-year and changed adherence in the second trial-year.

		MCID at year 1	ΔPDC (PDC year 2-PDC year 1)	Mean difference	P-value	Observations (N)
Improvement	CCQ	No	.1%	−2.4%	.326	437
		Yes	2.5%			
	SGRQ	No	2.0%	4.6%	**.038**	422
		Yes	−2.6%			
Deterioration	CCQ	No	1.3%	2.0%	.373	437
		Yes	−.7%			
	SGRQ	No	.8%	1.5%	.502	422
		Yes	−.7%			

HRQoL = health-related quality of life; MCID = Minimal Clinically Important Difference; CCQ: Clinical COPD Questionnaire; SGRQ: Saint George's Respiratory Questionnaire; PDC = Proportion of Days Covered, Unpaired t test, no MCID vs MCID.

3.3. Correcting for disease severity

When indicators of disease severity (FEV_1%pred, prior exacerbations, MRC dyspnoea score, Charlson comorbidity index) were added, the associations between adherence and HRQoL decreased, regardless of how we measured HRQoL (Table 2).

3.4. Correcting for healthy lifestyle

When further adding indicators of a healthy lifestyle in general (level of physical activity, self-efficacy and smoking status), we did not find a relationship between adherence and HRQoL either (Table 2).

3.5. Reversed causality

The PDC of patients with an improvement greater than or equal to the MCID in SGRQ score (i.e. ≥4 points) over the first trial-year decreased on average with 2.6% during the second trial-year year, whereas the PDC of patients without such an improvement increased with 2%, leading to a significant difference in change in PDC of 4.6% between these two groups (Table 3). This indicates that improved HRQoL may reduce future adherence. This association was found for the SGRQ but not for the CCQ, nor did we find an association between a clinically relevant deterioration in HRQoL and an improved adherence in the next year (Table 3). However, accounting for the previous HRQoL (using a linear model with unstructured covariance matrix for repeated measures), still did not result in the expected positive associations between adherence and HRQoL, regardless of how we measured HRQoL (Appendix 3).

3.6. Sensitivity analyses

The results of the sensitivity analyses to investigate the impact of changing the definition of adherence are presented in Appendix 4 to 7. Appendix 4 shows the results of the sensitivity analyses in which we used four categories of PDC (i.e. <60%, 60–79%, 80–99%, >99%). Patients with a PDC of 80–99% had a significantly higher SGRQ score than patients with a PDC <60%, indicating a worse HRQoL. This difference of 4.47 exceeds the MCID of 4 points on the SGRQ [21]. Also after correction for demographics and healthy lifestyle variables, patients with a PDC of 80–99% had a significantly higher SGRQ score than patients with a PDC <60%. After controlling for disease severity, patients with a PDC of 80–99% had no longer a significantly higher SGRQ score. Using PDC as a continuous variable, we did not find an association between adherence and HRQoL, independent of whether we corrected for demographics, healthy lifestyle and disease severity (Appendix 5). Neither did we find an association with adherence using the minimum PDC if patients used medication from different maintenance medication categories (Appendix 6). However, when using the maximum PDC if patients used medication from different maintenance medication categories, adherent patients had a significantly higher SGRQ and CCQ score than non-adherent patients, even after correcting for demographics (Appendix 7). These differences in the SGRQ score (5.75 and 4.81) exceed the MCID of 4 points but the differences in the CCQ score (.17 and .15) did not exceed the MCID of .4 points.

4. Discussion

This study investigated the association between medication adherence and HRQoL, thereby illustrating methodological challenges that need to be addressed. These challenges were the possibility of confounding by (i) disease severity, (ii) healthy lifestyle, (iii) and reversed causality. In unadjusted analyses, we found that adherent patients had a worse SGRQ score. This association disappeared when we corrected for healthy lifestyle and, especially, disease severity. This demonstrates the importance of this correction. However, after this correction we did not find that better adherence led to better HRQoL. We found some indications of reversed causality because an improvement in SGRQ score during the first year was associated with a reduction in adherence during the second year, whereas no improvement in SGRQ was associated with an increase in adherence.

The first challenge sought to determine the impact of correcting for disease severity. Our hypothesis was that more severely ill patients have a higher need for medication and as a result they are more likely to be adherent, thus making a correction for disease severity necessary when studying the association between adherence and HRQoL. Turner and colleagues [31] and Ingebrigtsen and colleagues [27] found that FEV1%pred was worse in the adherent group compared to the non-adherent group, while the FEV1%pred did not significantly differ between these groups in two other studies [32,33]. Previous studies also found that adherence in COPD was influenced by other indicators of disease severity; shortness of breath [27,31], exacerbations [27], and comorbidities such as depression [28,34]. We only found in the second year, that the adherent patients did have a worse MRC dyspnoea and SGRQ score than the non-adherent patients. Nevertheless, correction for disease severity with the variables FEV1%pred, exacerbations, MRC dyspnoea scale and Charlson comorbidity index removed the association between better adherence and worse SGRQ score in this study. Therefore, it is of important to accurately account for these indicators of COPD disease severity. Only one previous study [35] that investigated the influence of adherence in COPD medication on HRQol included an indicator of disease severity (depression) in their analyses. With correction for depression score, they found that better adherence was associated with improved HRQoL (SGRQ score). Unfortunately, they did not report results without this correction.

In the second challenge, we determined the impact of a

potential healthy-adherer effect. Our hypothesis was that those who take good care of their health in general (healthy lifestyle) are more likely to be adherent to medication, thus making it important to correct for differences in lifestyle. We did not find any statistically significant differences in smoking status, physical activity and self-efficacy between the adherent and non-adherent group. This was in accordance with, Turner and colleagues [31], who also found that the exercise level between the adherent and non-adherent group did not differ. In contrast, other studies did seem to be consistent with the "healthy-adherer" impact: the proportion of smokers [28,31,33] and drinkers [31] was lower among the adherer group and COPD patients with higher self-efficacy scores [28] were more likely to be classified as adherent.

The impact of correcting for indicators of a healthy lifestyle in our study depended on the definition of adherence. When we defined adherence as a PDC $\geq$80%, correction for lifestyle reduced the association between a better adherence and a worse SGRQ score and left it statistically non-significant. Still, the reduction of the association was markedly smaller than when we adjusted for disease severity. When we used categories for PDC-levels, patients with good adherence (PDC 80%–99%) still had a relatively bad average SGRQ score. We found similar results if we used the maximum PDC, i.e. good adherence was associated with worse CCQ and SGRQ scores even after correcting for healthy lifestyle variables.

In the third challenge, we investigated the presence of potential reversed causality. In line with Agh and colleagues [8], a better SGRQ score was predictive of decreased adherence to COPD medications during that year. However, accounting for previous HRQoL did not result in positive associations between adherence and HRQoL, regardless of how we measured HRQoL. It is plausible that more frequent measurements of HRQoL and clinical variables, combined with adherence calculations over shorter intervals, would lead to better estimates of the causal effect of adherence on HRQoL. Hence, it is likely that HRQoL at the end of each year was mainly affected by adherence in the weeks or months immediately prior to the measurement, and not as much by adherence over the full year. Similarly, adherence could have been influenced by current disease symptoms, more than by HRQoL in a more distant past.

We did not find a linear relationship between the degree of medication adherence and HRQoL. Patients with a PDC of 80–99% had a substantially and significantly worse SGRQ score than patients with a PDC below 60%, but patients with a PDC of $\geq$100% did not. None of the previous adherence studies in COPD performed analyses using various cut-off values to define adherence and only two studies [32,33] explained the reason for their cut-off value chosen. We advise further studies to perform sensitivity analysis with different subgroups of adherent levels, including a group with optimal- and over-users.

It was interesting that we have not found any association between adherence and the generic HRQoL instrument EQ-5D whereas we did find an association between adherence and the disease-specific HRQoL instruments (SGRQ and CCQ). These findings might be due to the fact that disease-specific questionnaires seem to be more sensitive in finding differences in symptoms that are not usually picked up by the generic instruments [36–38]. We therefore advise researchers to use disease-specific instruments when assessing the relationship between adherence and HRQoL.

Most previous studies on the association between adherence and health outcomes relied on proxies for disease severity because other indicators of disease severity (e.g. lung function) were lacking [13,39]. Using the RECODE study, we were able to use various indicators of disease severity. Moreover, we were able to investigate the association between adherence and both generic and disease-specific HRQoL. Furthermore, due to (i) the inclusion of RECODE patients from the intervention group as well as the control group and (ii) the repeated measurements of the patients, we included over 800 observations in our analyses.

This study has some limitations. One is that the adherence data of the present study were based on EMR. These data do not indicate whether a patient has actually filled the prescription and has subsequently taken the medication (appropriately). Hence, it is likely that adherence has been overestimated. Probably the only way to do it right is by using real-time medication monitoring inhalers, i.e. inhalers that send a signal to a data centre each time the button is pressed. Even then, you cannot be 100% sure that the medication is actually inhaled. However since this type of monitoring is still very costly and difficult to implement in real life we have to rely on proxy measures of adherence. Prescription data and pharmacy dispensing data are often used as proxies, and in our study we have used prescription data because it is generally more accurate than estimations from physicians and self-reports by patients [16]. In the Netherlands, a patient has to actively request a repeated prescription of maintenance medication, because physicians are not allowed to prescribe medication for more than 3 months of use. Furthermore, patients have to pay for these prescriptions, out-of-pocket, as long as the maximum amount of patient co-payment (currently €375 per year) has not been paid. This maximum amount of co-payment is obligatory. Hence, we can safely assume that there is a positive association between prescribing, dispensing and use of medication. Second, we did not evaluate the effect of medication overuse. This is an important issue for future research as we did not find a continuously positive relationship between the degree of medication adherence and HRQoL, i.e. those with medication overuse (PDC>99%) did not have a better HRQoL than those with a PCD<60%. Third, patients registered in primary care groups that had incomplete EMR with respect to medication could not be included in this study. However, this is due to the fact that we were not able to extract data on type of medication and dosage prescribed from all of the different EMR systems of the GPs and not an indication of a systematic difference between practices. Indeed, the baseline characteristics of the subset of RECODE patients in the current study were comparable to characteristics of the full RECODE dataset.

To conclude, we were unable to find a positive association between COPD medication adherence and HRQoL. Even after adjusting for potential confounders such as demographics, disease severity and healthy lifestyle variables, we did not find a positive relationship. Our analyses demonstrated that the lack of correction for disease severity and healthy lifestyle variables may even result in a reversed association; patients with good COPD medication adherence had a worse HRQoL compared to patients with poor COPD medication adherence. Further studies should improve the adjustment for disease severity and previous HRQoL, perhaps by using shorter intervals.

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Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.rmed.2015.11.008.

Appendices

Appendix 1
Baseline characteristics of this study compared to the total RECODE population.

Characteristic	Subset of RECODE population (N = 511)	Total RECODE population (N = 1.086)	P-value
Age (years) (SD)	68.0 (10.7)	68.3 (11.2)	.621
Male (%)	51.0	53.9	.235
Low education (%)	41.5	40.3	.684
FEV_1%pred	66.1	67.8	.123
Charlson comorbidity index (SD)	2.3 (1.2)	2.3 (1.3)	.421
Physical activity (MET minutes) (SD)	2.641 (4.241)	2.925 (4.683)	.247
Self-efficacy (SD)	65.2 (17.6)	65.3 (17.4)	.921
Current smoker (%)	37.3	36.7	.817
CCQ (SD)	1.47 (.94)	1.50 (.97)	.543
SGRQ (SD)	35.0 (20.3)	35.6 (20.5)	.568
EQ-5D utility (SD)	.74 (.27)	.74 (.26)	.852

SD = Standard Deviation; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MET = Metabolic Equivalent Time; CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Appendix 2
Proportion of days covered medication according to type of medication.

Year		N (%)	Proportion of days covered	Standard deviation
Year 0	Inhaled corticosteroids	73 (16)	79.3%	26.6%
	Long-acting muscarinic antagonists	56 (12)	76.3%	27.4%
	LABA/ICS combinations	312 (67)	79.1%	25.9%
	β2-agonists	285 (61)	86.1%	22.5%
	Overall	465 (100)	80.9%	23.5%
Year 1	Inhaled corticosteroids	79 (16)	77.9%	26.7%
	Long-acting muscarinic antagonists	75 (15)	78.2%	27.4%
	LABA/ICS combinations	354 (72)	74.7%	28.2%
	β2-agonists	310 (63)	81.6%	25.0%
	Overall	491 (100)	76.3%	25.4%
Year 2	Inhaled corticosteroids	75 (16)	77.9%	27.9%
	Long-acting muscarinic antagonists	76 (16)	79.4%	25.3%
	LABA/ICS combinations	331 (71)	76.2%	26.6%
	β2-agonists	298 (64)	82.4%	22.7%
	Overall	469 (100)	77.8%	24.0%

Appendix 3
Linear mixed models accounting for HRQoL in the previous year.

		β	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*	*β*	*P-value*
Dependent variable CCQ											
	Intercept	1.50	<.01	1.34	<.01	1.18	<.01	2.69	<.01	2.11	<.01
	Adherent (PDC ≥ 80%)	**.02**	**.77**	**−.003**	**.96**	**.01**	**.92**	**.03**	**.64**	**.07**	**.29**
Demographics	Year 2	.34	<.01	.34	<.01	.26	<.01	.35	<.01	.25	<.01
	Age			.0001	.98	−.004	.19	−.005	.32	−.01	.09
	Men			−.04	.62	.05	.50	−.04	.71	.07	.33
	Low education			.48	<.01	.29	<.01	.36	<.01	.21	<.01
Disease severity	FEV_1% pred					−.01	<.01			−.005	<.01
	Exacerbations					.09	<.01			.11	<.01
	MRC dyspnoea					.29	<.01			.31	<.01
	Charlson comorbidity index					.08	<.01			.03	.36
Healthy lifestyle	Physical activity (MET minutes)							−2.0e-5	.02	2.7e-6	.75
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.18	.04	.14	.06
	Observations used in the analysis (N)	825		754		726		542		524	
Dependent variable SGRQ											
	Intercept	35.3	<.01	28.0	<.01	30.4	<.01	49.9	<.01	42.9	<.01
	Adherent (PDC ≥ 80%)	**−.27**	**.82**	**−.27**	**.82**	**.30**	**.80**	**.85**	**.58**	**1.26**	**.36**
Demographics	Year 2	3.75	<.01	3.67	<.01	2.22	<.01	2.97	<.01	.89	.46
	Age			.07	.17	−.02	.83	.01	.88	−.05	.51
	Men			−2.72	<.01	−.73	.64	−3.07	.11	−.53	.72
	Low education			10.1	<.01	6.61	<.01	9.18	<.01	5.28	<.01
Disease severity	FEV_1% pred					−.21	<.01			−.17	<.01
	Exacerbations					1.73	<.01			2.93	<.01
	MRC dyspnoea					5.28	<.01			7.13	<.01
	Charlson comorbidity index					2.33	<.01			1.09	.08
Healthy lifestyle	Physical activity (MET minutes)							−.0002	.18	1.8e−4	.28
	Self-efficacy							−.29	<.01	−.23	<.01
	Smoker							1.19	.53	.09	.96
	Observations used in the analysis (N)	794		729		704		542		523	

Appendix 3 (*continued*)

		β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*
Dependent variable EQ-5D											
	Intercept	.72	<.01	.68	<.01	.77	<.01	.33	<.01	.56	<.01
	Adherent (PDC ≥ 80%)	**.002**	**.89**	**.004**	**.80**	**.01**	**.53**	**.006**	**.78**	**.01**	**.71**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.05	<.01	.06	<.01
	Age			.001	.47	.002	.10	.001	.21	.002	.13
	Men			.06	<.01	.04	.05	.07	<.01	.05	.02
	Low education			−.09	<.01	−.06	<.01	−.08	<.01	−.05	.02
Disease severity	FEV_1% pred					.0002	.67			−.0003	.59
	Exacerbations					−.02	.03			−.02	.03
	MRC dyspnoea					−.03	<.01			−.03	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							2.9e-7	.90	−3.3e-6	.16
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.01	.54	−.02	.32
	Observations used in the analysis (N)	827		760		733		555		535	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time, PDC = Proportion of Days Covered.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Appendix 4
Linear mixed models using four categories of PDC.

		β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*
Dependent variable CCQ											
	Intercept	1.46	<.01	1.38	<.01	1.17	<.01	2.72	<.01	1.85	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60–79%)	**−.01**	**.93**	**−.03**	**.75**	**.01**	**.95**	**.01**	**.90**	**.06**	**.53**
	Adherence (PDC 80–99%)	**.11**	**.21**	**.09**	**.33**	**.05**	**.49**	**.19**	**.07**	**.14**	**.09**
	Adherence (PDC >99%)	**.06**	**.58**	**.004**	**.97**	**−.05**	**.57**	**.02**	**.85**	**.03**	**.78**
Demographics	Time	.30	<.01	1.32	<.01	.22	<.01	.33	<.01	.21	<.01
	Age			.0001	.99	−.01	.02	−.005	.25	−.01	.05
	Men			−.03	.72	.08	.15	−.04	.60	.08	.23
	Low education			.45	<.01	.22	<.01	.35	<.01	.16	.03
Disease severity	FEV_1% pred					−.005	<.01			−.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.64
Healthy lifestyle	Physical activity (MET minutes)							−2.1e-5	.04	8.0e-6	.35
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.14	.09	.13	.06
	Observations used in the analysis (N)	825		754		542		542		524	
Dependent variable SGRQ											
	Intercept	32.9	<.01	25.0	<.01	21.7	<.01	59.1	<.01	40.2	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60–79%)	**.74**	**.75**	**−.24**	**.92**	**.07**	**.97**	**−.60**	**.81**	**.08**	**.97**
	Adherence (PDC 80–99%)	**5.15**	**.01**	**4.30**	**.03**	**2.24**	**.15**	**4.21**	**.05**	**2.79**	**.10**
	Adherence (PDC >99%)	**.93**	**.68**	**−.55**	**.81**	**−2.22**	**.20**	**−1.46**	**.55**	**−1.78**	**.35**
Demographics	Year 2	2.06	.18	2.39	.12	.63	.59	3.20	.08	.67	<.01
	Age			.09	.27	−.08	.18	−.03	.72	−.06	.35
	Men			−1.93	.22	.99	.41	−3.46	.04	.34	.80
	Low education			10.0	<.01	4.51	<.01	9.05	<.01	4.29	<.01
Disease severity	FEV_1% pred					−.11	<.01			−.15	<.01
	Exacerbations					3.46	<.01			3.67	<.01
	MRC dyspnoea					9.14	<.01			8.34	<.01
	Charlson comorbidity index					1.45	<.01			.89	.12
Healthy lifestyle	Physical activity (MET minutes)							−.0004	.02	.0002	.23
	Self-efficacy							−.37	<.01	−.23	<.01
	Smoker							−.40	.83	−.42	.77
	Observations used in the analysis (N)	794	729	704	542	925					
Dependent variable EQ-5D											
	Intercept	.72	<.01	.65	<.01	.79	<.01	.36	<.01	.64	<.01
	Adherence (PDC <60%)	**ref.**		**ref.**		**ref.**		**ref.**		**ref.**	
	Adherence (PDC 60–79%)	**−.004**	**.87**	**.01**	**.78**	**.02**	**.48**	**−.04**	**.23**	**−.03**	**.32**
	Adherence (PDC 80–99%)	**.008**	**.73**	**.01**	**.63**	**.02**	**.31**	**−.02**	**.45**	**−.01**	**.57**
	Adherence (PDC >99%)	**−.004**	**.86**	**.01**	**.60**	**.03**	**.18**	**.001**	**.98**	**.01**	**.61**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
	Age			.001	.22	.002	.01	.001	.29	.001	.16
	Men			.06	<.01	.04	.03	.07	<.01	.04	.02
	Low education			−.09	<.01	−.05	<.01	−.08	<.01	−.04	.02

(*continued on next page*)

Appendix 4 (*continued*)

		β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Disease severity	FEV_1% pred					−.0002	.62			−.001	.27
	Exacerbations					−.02	<.01			−.02	.02
	MRC dyspnoea					−.05	<.01			−.04	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							−8.5e-7	.72	−4.7e-6	.04
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.02	.37	−.03	.17
	Observations used in the analysis (N)	827		760		733		555		535	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; PDC = Proportion of Days Covered; ref = reference group; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Appendix 5
Linear mixed models using PDC as a continuous variable.

		β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Dependent variable CCQ											
	Intercept	1.40	<.01	1.28	<.01	1.20	<.01	2.68	<.01	1.84	<.01
	Adherence										
(PDC continuous)	**.14**	**.29**	**.07**	**.62**	**−.03**	**.80**	**.17**	**.30**	**.12**	**.34**	
Demographics	Year 2	.29	<.01	.30	<.01	.21	<.01	.32	<.01	.20	<.01
	Age			.0003	.94	−.01	.03	−.005	.24	−.01	.06
	Men			−.03	.69	.08	.16	−.04	.59	.08	.24
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV_1% pred					−.005	<.01			−.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.38	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.73
Healthy lifestyle	Physical activity (MET minutes)							−2.1e-5	.04	7.5e-6	.37
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.14	.11	.13	.07
	Observations used in the analysis (N)	825		754		726		542		524	
Dependent variable SGRQ											
	Intercept	31.4	<.01	23.7	<.01	22.5	<.01	59.0	<.01	40.8	<.01
	Adherence (PDC continuous)	**4.96**	**.11**	**2.86**	**.37**	**−.58**	**.81**	**1.86**	**.58**	**.34**	**.90**
Demographics	Year 2	1.94	.21	2.34	.13	.57	.63	2.93	.11	.35	.81
	Age			.09	.24	−.07	.22	−.03	.71	−.06	.38
	Men			−1.98	.21	.97	.42	−3.48	.04	−.37	.79
	Low education			10.1	<.01	4.64	<.01	9.32	<.01	4.50	<.01
Disease severity	FEV_1% pred					−.11	<.01			−.15	<.01
	Exacerbations					3.48	<.01			3.71	<.01
	MRC dyspnoea					9.15	<.01			8.37	<.01
	Charlson comorbidity index					1.37	<.01			.76	.19
Healthy lifestyle	Physical activity (MET minutes)							−.001	.01	.0002	.26
	Self-efficacy							−.37	<.01	−.22	<.01
	Smoker							−.62	.74	−.55	.70
	Observations used in the analysis (N)	794		729		704		542		523	
Dependent variable EQ-5D											
	Intercept	.70	<.01	.63	<.01	.77	<.01	.35	<.01	.62	<.01
	Adherence (PDC continuous)	**.03**	**.44**	**.04**	**.22**	**.06**	**.06**	**.01**	**.83**	**.02**	**.64**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
	Age			.001	.25	.002	.02	.001	.30	.001	.19
	Men			.06	<.01	.04	.03	.07	<.01	.04	.02
	Low education			−.09	<.01	−.05	<.01	−.08	<.01	−.05	.02
Disease severity	FEV_1% pred					−.0002	.68			−.001	.33
	Exacerbations					−.02	<.01			−.02	.02
	MRC dyspnoea					−.05	<.01			−.04	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							−6.8e-7	.78	−4.6e-6	.05
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.02	.37	−.03	.17
	Observations used in the analysis (N)	827		760		733		555		535	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; PDC = Proportion of Days Covered; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Appendix 6
Linear mixed models using the **minimum** PDC if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations)

		β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Dependent variable CCQ											
	Intercept	1.48	<.01	1.23	<.01	1.10	<.01	2.72	<.01	1.85	<.01
	Adherent (PDC ≥ 80%)	.06	.41	.03	.70	.01	.89	.04	.61	.04	.50
	Year 2	.20	<.01	.30	<.01	.22	<.01	.32	<.01	.21	<.01
Demographics	Age			.001	.65	−.01	.07	−.004	.35	−.01	.10
	Men			−.04	.53	.07	.23	−.05	.50	.07	.29
	Low education			.45	<.01	.22	<.01	.36	<.01	.16	.02
Disease severity	FEV1% pred					−.01	<.01			−.005	.01
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.37	<.01			.36	<.01
	Charlson comorbidity index					.06	<.01			.01	.63
Healthy lifestyle	Physical activity (MET minutes)							−2.3e-5	.02	6.0e-6	.48
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.14	.11	.13	.06
	Observations used in the analysis (N)	817		748		720		537		519	
ependent variable SGRQ											
	Intercept	33.9	<.01	23.3	<.01	20.6	<.01	58.6	<.01	39.6	<.01
	Adherent (PDC ≥ 80%)	2.22	.15	1.46	.35	.16	.90	2.90	.69	.44	.74
Demographics	Year 2	2.10	.18	2.41	.12	.65	.59	2.90	.11	.37	.80
	Age			.12	.13	−.05	.40	−.02	.86	−.05	.50
	Men			−2.30	.15	.72	.55	−3.67	.03	−.47	.73
	Low education			10.2	<.01	4.69	<.01	9.32	<.01	4.48	<.01
Disease severity	FEV_1% pred					−.12	<.01			−.15	<.01
	Exacerbations					3.51	<.01			3.76	<.01
	MRC dyspnoea					9.09	<.01			8.34	<.01
	Charlson comorbidity index					1.40	<.01			.80	.17
Healthy lifestyle	Physical activity (MET minutes)							−.001	.01	.0002	.31
	Self-efficacy							−.36	<.01	−.22	<.01
	Smoker							−.57	.76	−.48	.74
	Observations used in the analysis (N)	786		723		698		537		518	
EQ-5D											
	Intercept	.71	<.01	.68	<.01	.82	<.01	.37	<.01	.65	<.01
	Adherent (PDC ≥ 80%)	**.01**	**.66**	**.01**	**.44**	**.02**	**.21**	**.01**	**.78**	**.01**	**.62**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
	Age			.001	.45	.002	.05	.001	.38	.001	.26
	Men			.07	<.01	.04	<.01	.07	<.01	.05	.01
	Low education			−.09	<.01	−.05	<.01	−.08	<.01	−.05	.01
Disease severity	FEV_1% pred					−.0001	.74			−.0005	.35
	Exacerbations					−.02	<.01			−.02	.02
	MRC dyspnoea					−.05	<.01			−.04	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							−4.6e-8	.99	−3.9e-6	.10
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.02	.31	−.03	.13
	Observations used in the analysis (N)	819		754		727		550		530	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; PDC = Proportion of Days Covered; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

Appendix 7
Linear mixed models using the **maximum** PDC if patients used medications from different maintenance medication categories (LABA, LAMA, ICS, LABA/ICS combinations).

		β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Dependent variable CCQ											
	Intercept	1.39	<.01	1.21	<.01	1.11	<.01	2.66	<.01	1.81	<.01
	Adherent (PDC ≥ 80%)	**.17**	**.02**	**.15**	**.05**	**.04**	**.52**	**.17**	**.05**	**.12**	**.09**
Demographics	Year 2	.30	<.01	.30	<.01	.21	<.01	.32	<.01	.20	<.01
	Age			.001	.87	−.01	.05	−.005	.26	−.01	.06
	Men			−.03	.65	.08	.19	−.04	.64	.08	.22
	Low education			.45	<.01	.22	<.01	.35	<.01	.16	.02
Disease severity	FEV_1% pred					−.01	<.01			−.004	.02
	Exacerbations					.15	<.01			.14	<.01
	MRC dyspnoea					.37	<.01			.37	<.01
	Charlson comorbidity index					.06	.01			.01	.75
Healthy lifestyle	Physical activity (MET minutes)							−2.2e-5	.03	6.3e-6	.47
	Self-efficacy							−.02	<.01	−.01	<.01
	Smoker							.14	.09	.14	.06
	Observations used in the analysis (N)	818		749		721		542		520	

(*continued on next page*)

Appendix 7 (*continued*)

		β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*	β	*P-value*
Dependent variable SGRQ											
	Intercept	31.1	<.01	22.3	<.01	22.2	<.01	57.2	<.01	38.7	<.01
	Adherent (PDC ≥ 80%)	**5.75**	**<.01**	**4.81**	**<.01**	**1.43**	**.27**	**3.34**	**.06**	**1.87**	**.19**
Demographics	Year 2	2.19	.15	2.41	.12	.62	.60	2.89	.11	.38	.79
	Age			.10	.22	−.06	.32	−.03	.76	−.06	.42
	Men			−2.13	.17	.80	.51	−3.43	.05	−.34	.81
	Low education			9.99	<.01	4.70	<.01	9.14	<.01	4.41	<.01
Disease severity	FEV_1% pred					−.11	<.01			−.15	<.01
	Exacerbations					3.51	<.01			3.76	<.01
	MRC dyspnoea					9.09	<.01			8.37	<.01
	Charlson comorbidity index					1.36	<.01			.73	.20
Healthy lifestyle	Physical activity (MET minutes)							−.001	.01	.0002	.30
	Self-efficacy							−.36	<.01	−.22	<.01
	Smoker							−.48	.79	−.45	.76
	Observations used in the analysis (N)	820		724		699		538		519	
Dependent variable EQ-5D											
	Intercept	.72	<.01	.69	<.01	.82	<.01	.39	<.01	.66	<.01
	Adherent (PDC ≥ 80%)	**−.01**	**.65**	**−.004**	**.82**	**.02**	**.34**	**−.01**	**.63**	**.001**	**.96**
Demographics	Year 2	.07	<.01	.06	<.01	.07	<.01	.06	<.01	.07	<.01
	Age			.001	.43	.002	.05	.001	.40	.001	.28
	Men			.07	<.01	.04	<.01	.07	<.01	.05	.01
	Low education			−.09	<.01	−.05	<.01	−.08	<.01	−.05	.01
Disease severity	FEV_1% pred					−.0001	.81			−.0005	.36
	Exacerbations					−.02	<.01			−.02	.02
	MRC dyspnoea					−.05	<.01			−.04	<.01
	Charlson comorbidity index					−.04	<.01			−.03	<.01
Healthy lifestyle	Physical activity (MET minutes)							−5.3e-8	.98	−4.0e-6	.09
	Self-efficacy							.005	<.01	.004	<.01
	Smoker							−.02	.33	−.03	.14
	Observations used in the analysis (N)	820		755		728		551		531	

CCQ = Clinical COPD Questionnaire; SGRQ = Saint George's Respiratory Questionnaire; EQ-5D = EuroQoL 5-Dimensions; PDC = Proportion of Days Covered; FEV_1% pred = predicted percentage of Forced Expiratory Volume in 1 s; MRC = Medical Research Council; IPAQ = International Physical Activity Questionnaire; MET = Metabolic Equivalent Time.
Note: a higher score on SGRQ & CCQ indicates a worse HRQoL, whereas a higher score on EQ-5D indicates a better HRQoL.

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